Peer Review
Experimental Toxicology Division
N H E E R L

CUMULATIVE RISK

Pharmacokinetics of Type II Pyrethroids for Cumulative Risk Assessment

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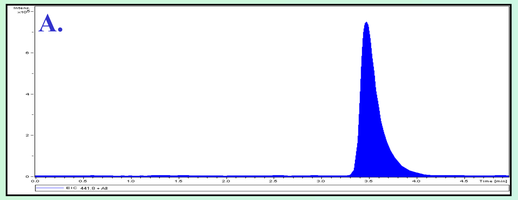
Introduction

Pyrethroid insecticides are increasing in use as certain organophosphate insecticides are being phased out. Pyrethroids are a class of insecticides which act as neurotoxicants via the modulation of nerve axon sodium channels in the central and peripheral nervous systems. Pyrethroids have many different applications in agriculture, forestry, horticulture, public health, and in homes. Because of their widespread use the potential for human exposure is high. Under the Food Quality Protection Act (FQPA) of 1996 the EPA is required to take into account the cumulative risk assessment of pesticides which act by a common mode of action. Because pyrethroids appear to have a common mode of action cumulative risk assessment may be necessary. Pyrethroids are commonly separated into two types (Type I and Type II) based on chemical structure. Type I pyrethroids lack a cyano moiety while Type II pyrethroids contain a cyano moiety. This work will mainly focus on the Type II pyrethroids and will involve determination of *in vivo* pharmacokinetic parameters of individual type II pyrethroids. These results will then be compared to the pharmacokinetics of environmentally relevant mixtures of Type II pyrethroids. These studies will be done in conjunction with neurotoxicology studies of these same pyrethroids and mixtures. This will allow us to compare tissue dose with behavioral alterations in order to understand the relationship between exposure, dose, and response. In addition to the *in vivo* studies *in vitro* work will be done with human and animal tissue to assess species differences in metabolism and aid in species to species extrapolation of risk. This will provide in part data to assess the cumulative risk of the pyrethroid insecticides.

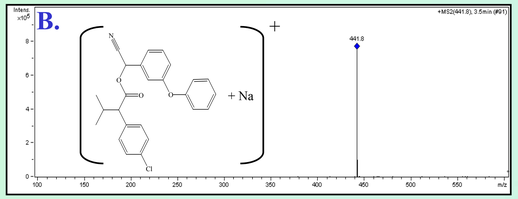
Methods

These studies will be conducted in adult male rats. At lease two doses, and 7 time points will be evaluated. Animals will be dosed either orally or by IV injection and will receive type II pyrethroids individually or in environmentally relevant mixtures. Tissues including the brain, liver, fat, kidney, muscle, and blood will be evaluated. Tissue concentrations will be determined using and LC/MS-MS methodology. In addition i*n vitro* studies will be done with human and animal tissues, potentially using hepatocyte cultures and/or serum or plasma.

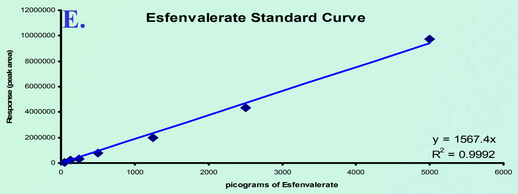
Results



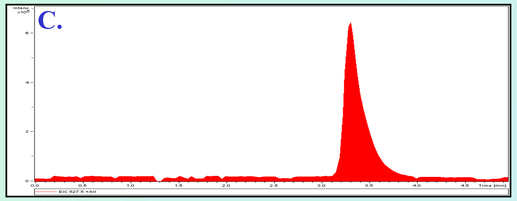
A. Mass Spec Chromatogram of Esfenvalerate. Extracted Ion Current for m/z 441.8 @ 3.5min



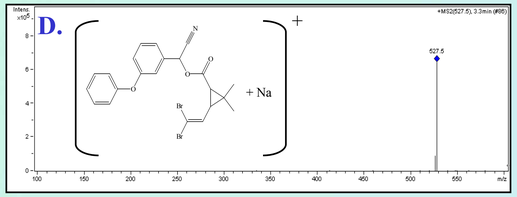
B. Mass Spectrum of Esfenvalerate m/z = 441.8. Sodium adduct of parent compound..



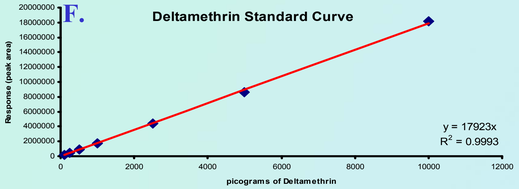
E. Standard Curve of Esfenvalerate. 50-5000 picograms



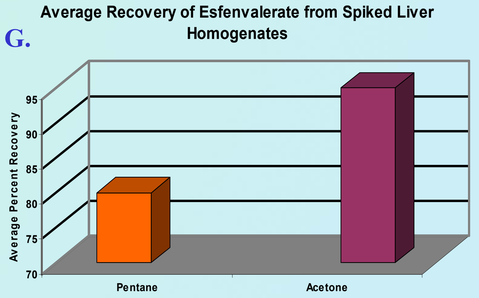
C. Mass Spec Chromatogram of Deltamethrin. Extracted Ion Current for m/z 527.5 @ 3.3min



D. Mass Spectrum of Deltamethrin m/z = 527.5. Sodium adduct of parent compound.



F. Standard Curve of Deltamethrin. 100-10000 picograms



G. Comparison of extraction efficiency with two different solvents

H. In Vitro Metabolic Parameters of Deltamethrin

Km	Vmax
53.8nM	185pmoles/min/mg

H. In Vitro Kinetic parameters for the metabolism of deltamethrin by rat liver microsomes determined using the new LC/MS methodology.

Conclusions and Impact

To date a working tissue extraction procedures and LC/MS methods have been developed for deltamethrin and esfenvalerate. With these methods we can now proceed with the *in vitro* and *in vivo* studies for deltamethrin and esfenvalerate.

The results of this project will ultimately lead to a better understanding of the potential human health risks associated with cumulative exposure to pyrethroid pesticides.

Future Directions

Mass Spec and extraction methods must first be validated for all tissue and media types to be used in the *in vitro* and *in vivo* pharmacokinetic studies for eight different pyrethroids. *In vitro* studies will be completed first and used in conjunction with a PBPK model in an effort to develop predictive pharmacokinetic models. These models will reduce the number of animals and samples required to complete *in vivo* studies. Individual and mixture studies will then be done using the type II pyrethroids. The final aspect of this work will be mixture studies with type II and type I pyrethroids.

SOLVING AGENCY PROBLEMS